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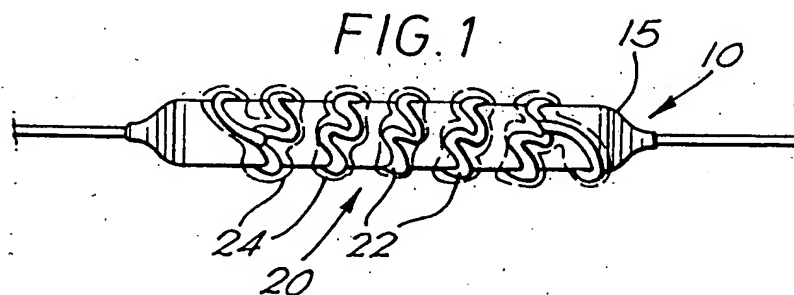
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(54) **Intraluminal stent.**

(57) An intraluminal stent comprising fibrin is capable of reducing the incidence of restenosis at the site of vascular injury such as that produced by an angioplasty procedure.



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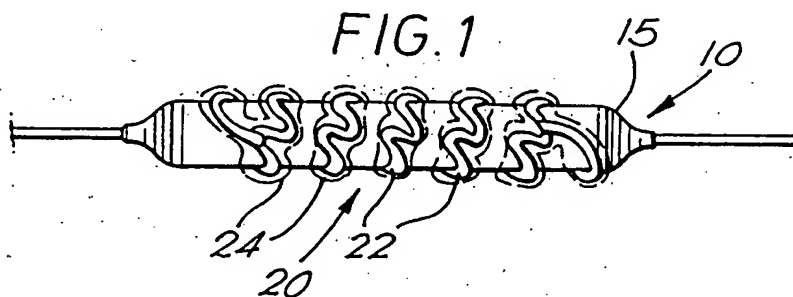
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This invention relates to intraluminal stents which can be used to reduce restenosis of body lumens and to methods of making such intraluminal stents.

Restenosis is the closure of a peripheral or coronary artery following trauma to the artery caused by efforts to open an occluded portion of the artery, such as, for example, by dilation, ablation, atherectomy or laser treatment of the artery. For these angioplasty procedures, restenosis occurs at a rate of about 20-50% depending on the vessel location, lesion length and a number of other variables. Restenosis is believed to be a natural healing reaction to the injury of the arterial wall that is caused by angioplasty procedures. The healing reaction begins with the clotting of blood at the site of the injury. The final result of the complex steps of the healing process is intimal hyperplasia, the migration and proliferation of medial smooth muscle cells, until the artery is again stenotic or occluded.

In an attempt to prevent restenosis, metallic intravascular stents have been permanently implanted in coronary or peripheral vessels. The stent is typically inserted by catheter into a vascular lumen and expanded into contact with the diseased portion of the arterial wall, thereby providing internal support for the lumen. However, it has been found that restenosis can still occur with such stents in place. Also, the stent itself can cause undesirable local thrombosis. To address the problem of thrombosis, persons receiving stents also receive extensive systemic treatment with anticoagulant and antiplatelet drugs.

To address the restenosis problem, it has been proposed to provide stents which are seeded with endothelial cells (Dichek, D.A. et al Seeding of Intravascular Stents With Genetically Engineered Endothelial Cells; *Circulation* 1989; 80: 1347-1353). In that experiment, sheep endothelial cells that had undergone retrovirus-mediated gene transfer for either bacterial beta-galactosidase or human tissue-type plasminogen activator were seeded onto stainless steel stents and grown until the stents were covered. The cells were therefore able to be delivered to the vascular wall where they could provide therapeutic proteins. Other methods of providing therapeutic substances to the vascular wall by means of stents have also been proposed such as in international patent application WO 91/12779 "Intraluminal Drug Eluting Prosthesis" and international patent application WO 90/13332 "Stent With Sustained Drug Delivery". In those applications, it is suggested that antiplatelet agents, anticoagulant agents, antimicrobial agents, antimetabolic agents and other drugs could be supplied in stents to reduce the incidence of restenosis.

In the vascular graft art, it has been noted that fibrin can be used to produce a biocompatible surface. For example, in an article by Soldani et al., "Bioartificial Polymeric Materials Obtained from Blends of Synthetic Polymers with Fibrin and Collagen" International

Journal of Artificial Organs, Vol. 14, No. 5, 1991, polyurethane is combined with fibrinogen and cross-linked with thrombin and then made into vascular grafts. In vivo tests of the vascular grafts reported in the article indicated that the fibrin facilitated tissue ingrowth and was rapidly degraded and reabsorbed. Also, published European Patent Application 0366564 applied for by Terumo Kabushiki Kaisha, Tokyo, Japan, discloses a medical device such as an artificial blood vessel, catheter or artificial internal organ is made from a polymerized protein such as fibrin. The fibrin is said to be highly nonthrombogenic and tissue compatible and promotes the uniform propagation of cells that regenerates the intima. Also, in an article by Gusti et al., "New Biolized Polymers for Cardiovascular: Applications", *Life Support Systems*, Vol. 3, Suppl. 1, 1986, "biolized" polymers were made by mixing synthetic polymers with fibrinogen and cross-linking them with thrombin to improve tissue ingrowth and neointima formation as the fibrin biodegrades. Also, in an article by Haverich et al., "Evaluation of Fibrin Seal in Animal Experiments", *Thoracic Cardiovascular Surgeon*, Vol. 30, No. 4, pp. 215-22, 1982, the authors report the successful sealing of vascular grafts with fibrin. However, none of these teach that the problem of restenosis could be addressed by the use of fibrin and, in fact, conventional treatment with anticoagulant drugs following angioplasty procedures is undertaken because the formation of blood clots (which include fibrin) at the site of treatment is thought to be undesirable.

However, surprisingly, it has now been found that an intraluminal stent comprising fibrin is capable of reducing the incidence of restenosis at the site of a vascular injury and can also serve as a matrix for the local administration of drugs to the site of a vascular injury. Fibrin is a naturally occurring bioabsorbable polymer of fibrinogen that arises during blood coagulation. As set forth above, antiplatelet and anticoagulant agents are thought to be desirable to prevent thrombosis (and to thereby prevent fibrin formation) in the lumen at the site of dilation or other treatment. By contrast, it has now been found that providing fibrin at the site of treatment can provide a readily tolerated, bioabsorbable surface which will interact in a natural manner with the body's healing mechanism and reduce the prospect for the intimal hyperplasia that causes restenosis.

Thus viewed from one aspect the invention provides an intraluminal stent comprising fibrin.

A stent according to the present invention can be made in virtually any configuration and can be delivered conventionally by catheter to the site of the luminal closure or restriction.

Viewed from a further aspect therefore the invention also provides a stent assembly comprising a patent according to the invention, and a catheter having at a distal end a balloon, the stent being mounted on

the outer surface of the balloon, and preferably being affixed thereto, e.g. with adhesive.

The stent may be fabricated by any convenient method but typically is manufactured by depositing fibrin on a stent substrate, e.g. by polymerization at or about the substrate or by attachment of a fibrin pre-form (e.g. a film) to the substrate or by polymerizing fibrin in an appropriate vessel, e.g. a cylindrical vessel optionally containing a central core member whereby to generate a cylindrical polymer fibrin mass and optionally forming the polymer mass into a desired shape.

Thus viewed from one further aspect the invention provides a method for making an intraluminal stent, the method comprising depositing fibrin on a stent substrate.

Viewed from a still further aspect the invention also provides a method for making an intravascular device from fibrin comprising the steps of:

- (a) admixing fibrinogen with a coagulating protein to produce fibrin;
- (b) neutralizing the coagulating protein, and
- (c) incubating the fibrin in a biological buffer solution.

Viewed from a still further aspect the invention provides the use of fibrinogen or fibrin for the manufacture of means for use in combatting restenosis or thrombosis.

The term "stent" as used herein means any device which when placed into contact with a site in the wall of a lumen to be treated, will also place the fibrin at the lumen wall and retain it at the lumen wall. This can include especially devices delivered percutaneously to treat coronary artery occlusions and to seal dissections or aneurysms of splenic, carotid, iliac and popliteal vessels.

The term "fibrin" as used herein means the polymer of fibrinogen that is produced during blood coagulation.

Blood coagulation generally requires the participation of several plasma protein coagulation factors: factors XII, XI, IX, X, VIII, VII, V, XIII, prothrombin, and fibrinogen, in addition to tissue factor (factor III), kallikrein, high molecular weight kininogen, Ca^{2+} , and phospholipid. The final event is the formation of an insoluble, cross-linked polymer, fibrin, generated by the action of thrombin on fibrinogen. Fibrinogen has three pairs of polypeptide chains (ALPHA 2 - BETA 2 - GAMMA 2) covalently linked by disulfide bonds with a total molecular weight of about 340,000. Fibrinogen is converted to fibrin through proteolysis by thrombin. An activation peptide, fibrinopeptide A (human) is cleaved from the amino-terminus of each ALPHA chain; fibrinopeptide B (human) from the amino-terminus of each BETA chain. The resulting monomer spontaneously polymerizes to a fibrin gel. Further stabilization of the fibrin polymer to an insoluble, mechanically strong form, requires cross-linking by

factor XIII. Factor XIII is converted to XIIIa by thrombin. XIIIa cross-links the GAMMA chains of fibrin by transglutaminase activity, forming EPSILON - (GAMMA - glutamyl) lysine cross-links. The ALPHA chains of fibrin also may be cross-linked.

Since fibrin blood clots are naturally subject to fibrinolysis as part of the body's repair mechanism, implanted fibrin can be rapidly biodegraded. Plasminogen is a circulating plasma protein that is adsorbed onto the surface of the fibrin polymer. The adsorbed plasminogen is converted to plasmin by plasminogen activator released from the vascular endothelium. The plasmin will then break down the fibrin into a collection of soluble peptide fragments.

Methods for making fibrin and forming it into implantable devices are well known as set forth in the following patents and published applications which are hereby incorporated by reference. In U.S. Patent 4,548,736 issued to Muller et al., fibrin is clotted by contacting fibrinogen with a fibrinogen-coagulating protein such as thrombin, reptilase or ancrod. Preferably, the fibrin in the stent of the present invention has Factor XIII and calcium present during clotting, as described in U.S. Patent 3,523,807 issued to Gerendas, or as described in published European Patent Application 0366564, in order to improve the mechanical properties and biostability of the implanted device. Also preferably, the fibrinogen and thrombin used to make fibrin in the present invention are from the same animal or human species as that in which the stent of the present invention will be implanted in order to avoid cross-species autoimmune reactions. In the Muller patent, the fibrin product is in the form of a fine fibrin film produced by casting the combined fibrinogen and thrombin in a film and then removing moisture from the film osmotically through a moisture permeable membrane. In the European Patent Application 0366564, a substrate (preferably having high porosity or high affinity for either thrombin or fibrinogen) is contacted with a fibrinogen solution and with a thrombin solution. The result is a fibrin layer formed by polymerization of fibrinogen on the surface of the device. Multiple layers of fibrin applied by this method could provide a fibrin layer of any desired thickness. Or, as in the Gerendas patent, the fibrin can first be clotted and then ground into a powder which is mixed with water and stamped into a desired shape in a heated mold. Increased stability can also be achieved in the shaped fibrin by contacting the fibrin with a fixing agent such as glutaraldehyde or formaldehyde. These and other methods known by those skilled in the art for making and forming fibrin may be used in the present invention.

Preferably the coagulating effect of any residual coagulation protein in the fibrin should be neutralized before employing it in the stent of the present invention in order to prevent clotting at the fibrin interface with blood after stent implantation. This can be ac-

complished, for example, by treating the fibrin with irreversible coagulation inhibitor compounds after polymerization. For example, hirudin or D-phenylalanylpropyl-arginine chloromethyl ketone (PPACK) could be used. Anti-coagulants such as heparin can also be added to reduce the possibility of further coagulation.

Polymeric materials can also be intermixed in a blend or co-polymer with the fibrin to produce a material with the desired properties of fibrin with improved structural strength. For example, the polyurethane material described in the article by Soldani et al., "Bioartificial Polymeric Materials Obtained from Blends of Synthetic Polymers with Fibrin and Collagen" International Journal of Artificial Organs, Vol. 14, No. 5, 1991, could be sprayed onto a suitable stent structure. Suitable polymers could also be biodegradable polymers such as polyphosphate ester, polyhydroxybutyric valerate (PHBV) and the like.

In U.S. Patent 4,548,736 issued to Muller et al., a fibrin composition is disclosed which can be a bioabsorbable matrix for delivery of drugs to a patient. Such a fibrin composition can also be used in the present invention by incorporating a drug or other therapeutic substance useful in diagnosis or treatment of body lumens to the fibrin provided on the stent. The drug, fibrin and stent can then be delivered to the portion of the body lumen to be treated where the drug may elute to affect the course of restenosis in surrounding luminal tissue. Examples of drugs that are thought to be useful in the treatment of restenosis are disclosed in published international patent application WO 91/12779 "Intraluminal Drug Eluting Prosthesis" which is incorporated herein by reference. Therefore, useful drugs for treatment of restenosis and drugs that can be incorporated in the fibrin and used in the present invention can include drugs such as anticoagulant drugs, antiplatelet drugs, antimetabolite drugs, anti-inflammatory drugs and antimitotic drugs. Such therapeutic substances can also be microencapsulated prior to their inclusion in the fibrin. The microcapsules then control the rate at which the therapeutic substance is provided to the blood stream or the body lumen. This avoids the necessity for dehydrating the fibrin as set forth in Muller et al., since a dense fibrin structure would not be required to contain the therapeutic substance and limit the rate of delivery from the fibrin. For example, a suitable fibrin matrix for drug delivery can be made by adjusting the pH of the fibrinogen to below about pH 6.7 in a saline solution to prevent precipitation (e.g., NaCl, CaCl₂, etc.), adding the microcapsules, treating the fibrinogen with thrombin and mechanically compressing the resulting fibrin into a thin film. The microcapsules which are suitable for use in this invention are well known. For example, the disclosures of U.S. Patent No. 4,897,268; 4,675,189; 4,542,025; 4,530,840; 4,389,330; 4,622,244; 4,464,317; and 4,943,449

could be used.

As discussed above, in one embodiment the stent of the invention can have an underlying polymeric or metallic structural element, a "stent substrate", onto which the fibrin is applied. In another embodiment the stent can be a composite of fibrin intermixed with a polymer. For example, a deformable metal wire stent such as that disclosed in U.S. Patent 4,886,082 issued to Wiktor could be coated with fibrin as set forth above in one or more coats (i.e. polymerization of fibrin on the metal framework by application of a fibrinogen solution and a solution of a fibrinogen-coagulating protein) or provided with an attached fibrin preform such as an encircling film of fibrin made as set forth above (i.e. a cast film as set forth in the Muller et al. patent). The stent and fibrin could then be placed onto the balloon at a distal end of a balloon catheter and delivered by conventional percutaneous means (e.g. as in an angioplasty procedure) to the site of the restriction or closure to be treated where it would then be expanded into contact with the body lumen by inflating the balloon. The catheter can then be withdrawn, leaving the fibrin stent of the present invention in place at the treatment site. The stent may therefore provide both a supporting structure for the lumen at the site of treatment and also a structure supporting the secure placement of fibrin at the lumen wall.

Preferred embodiments of the invention will now be described by way of Example and with reference to the accompanying drawings, in which:

Fig. 1 is a elevational view of a balloon catheter with a stent according to the present invention comprising a metallic substrate with a fibrin coating;

Fig. 2 is a elevational view of a balloon catheter with a stent according to the present invention comprising a metallic substrate provided with a fibrin film;

Fig. 3 is an elevational view of a fibrin incorporating polymeric stent according to the present invention; and

Figs. 4 to 10 are schematic illustrations of a method of making a stent according to the present invention.

Referring to Figure 1 there is shown a stent according to the invention in place on a balloon catheter. The catheter 10 has a balloon 15 upon which a stent 20 has been placed, the stent 20 having a deformable metal portion 22 and a fibrin coating 24 thereon. Fig. 2 shows an alternative stent 30 in which a fibrin film 32 has been affixed to the underlying metallic framework 34, e.g. by wrapping the film 32 around the framework 34 and securing the film 32 to the framework 34 (e.g. with an adhesive materials so that the film 32 will stay on the balloon 36 and framework 34 until it is delivered to the site of treatment. The film 32 is preferably wrapped over the framework 34 with folds or

wrinkles that will allow the stent 30 to be readily expanded into contact with the wall of the lumen to be treated.

Also, for example, a self-expanding stent of resilient polymeric material such as that disclosed in published international patent application WO 91/12779 "Intraluminal Drug Eluting Prosthesis" could be used in which fibrin is coated onto the stent or incorporated within the polymeric material of the stent. A stent of this general configuration is shown in Fig. 3. The stent 40 has a first set of filaments 42 which are helically wound in one direction and a second set of filaments 44 which are helically wound in a second direction. Any or all of these filaments 42, 44 could be fibrin and/or a blend of fibrin with another polymer. The combination of fibrin with another polymer may be preferred to provide improved mechanical properties and manufacturability for the individual filaments 42, 44. A suitable material for fibrin-containing filaments 42, 44 is the crosslinked blend of polyurethane and fibrin used as a vascular graft material in the article by Soldani et al., "Bioartificial Polymeric Materials Obtained from Blends of Synthetic Polymers with Fibrin and Collagen" International Journal of Artificial Organs, Vol. 14, No. 5, 1991. Other biostable or bioresorbable polymers could also be used. A fibrin-containing stent of this configuration can be affixed to the distal end of a catheter in a longitudinally stretched condition which causes the stent to decrease in diameter. The stent is then delivered through the body lumen on the catheter to the treatment site where the stent is released from the catheter to allow it to expand into contact with the lumen wall. It will be apparent to those skilled in the art that other self-expanding stent designs (such as resilient metal stent designs) could also be used with fibrin either incorporated in the material of the underlying structure of the stent or coated on the underlying structure of the stent.

A preferred method of making a stent according to the present invention is illustrated by Figs. 4-10. Fig. 4 is an elevational view of a stent and rigid tube into which the stent is inserted. Fig. 5 is an elevational view of the tube of Fig. 4 into which a catheter balloon is inserted. Fig. 6 is partial sectional view of the tube of Fig. 5 with included stent and catheter. Fig. 7 is a partial sectional view of the tube of Fig. 6 to which fibrin has been added. Fig. 8 is a partial sectional view of the tube of Fig. 7 in which the balloon has been expanded. Fig. 9 is an elevational view of the resulting stent being removed from the tube of Fig. 8. Fig. 10 is an elevational view of the completed stent mounted on the balloon of a catheter.

Referring to Figures 4 to 10, a stent 50 of the type disclosed in United States Patent 4,886,062 issued to Wiktor is inserted into a tube 55 which is preferably made from a rigid material and which has an inside diameter which is large enough to accommodate an un-

expanded PTCA balloon but which is smaller than a fully inflated PTCA balloon. APTCA balloon 60 attached to a catheter 62 and inflation device (not shown) is inserted into the stent 50 and tube 55. Fibrinogen at a pH of about 6.5, suspended in a saline solution, and thrombin are inserted into the tube 55 around the deflated balloon 60 and stent 50. The amount of thrombin added is not critical but preferably will polymerize the fibrinogen to fibrin 65 in about 5 minutes. After polymerization, the fibrin is allowed to crosslink for about an hour. The balloon 60 is then inflated to compress the fibrin 65 between the balloon 60 and tube 55. The balloon 60 is then deflated and removed from the tube 55. The resulting fibrin stent 70 includes the stent 50 embedded in a very thin elastic film of fibrin 65. The fibrin stent 70 may then be removed from the tube 55 and washed in a buffered saline solution. Further processing of the fibrin stent can also be undertaken to neutralize thrombin with PPACK or hirudin; to add anticoagulants such as heparin; to further facilitate crosslinking by incubation at body temperature in a biological buffer such as a solution of blood serum buffered by 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES); or to add plasticizers such as glycerol. The resulting fibrin stent can then be placed over a balloon, and secured onto the balloon by crimping. The stent can then be delivered transluminally and expanded into place in the body lumen by conventional procedures.

In a variant of this procedure, the metal stent portion may be eliminated to make a fibrin tube which can be placed on a balloon catheter and expanded into place in a body lumen. The absence of permanently implanted metal elements would allow the entire stent to biodegrade as healing is completed in the body lumen.

Claims

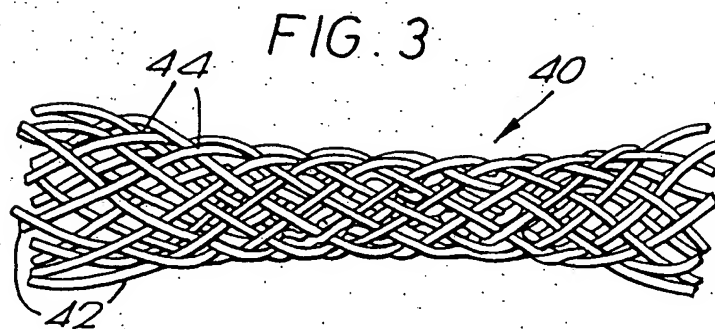
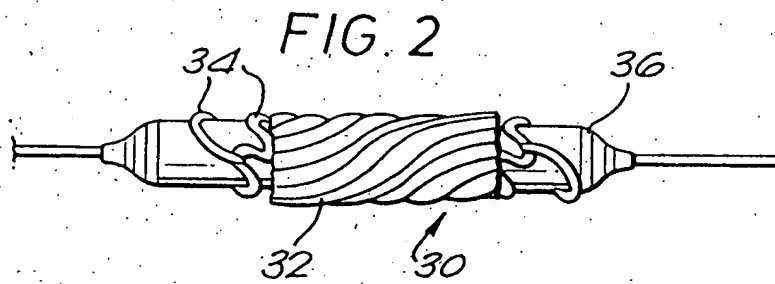
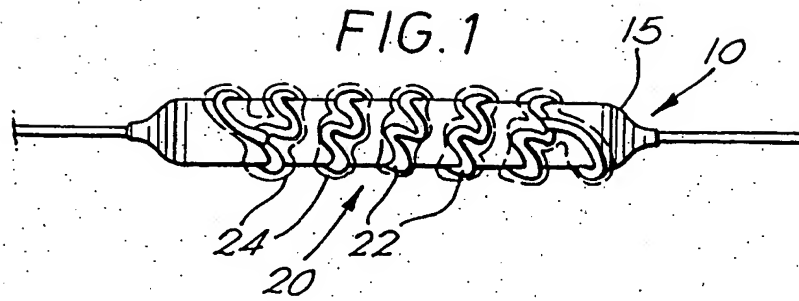
1. An intraluminal stent (20) comprising fibrin (24).
2. A stent as claimed in claim 1 having an underlying structure (22) of a deformable material.
3. A stent as claimed in claim 2 wherein said deformable material is a metal.
4. A stent as claimed in either of claims 2 and 3 wherein said deformable material is embedded in the fibrin.
5. A stent (30) as claimed in either of claims 2 and 3 wherein the fibrin is in a film (32) on said deformable material (34).
6. A stent as claimed in any one of claims 1 to 5 wherein the fibrin is intermixed with a polymeric

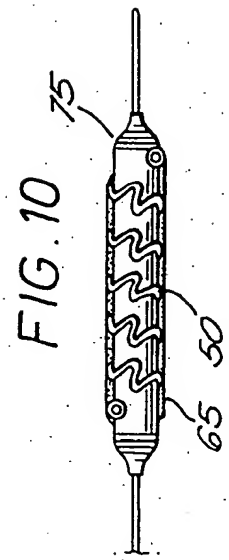
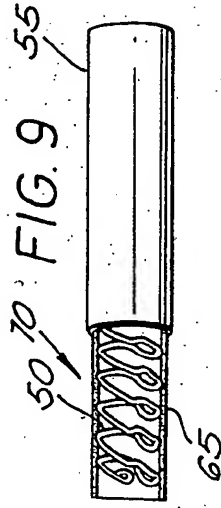
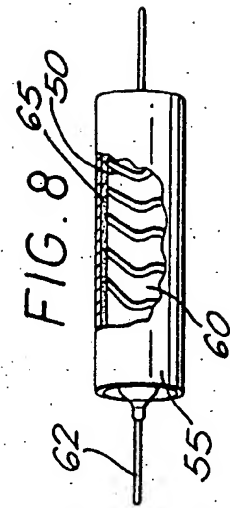
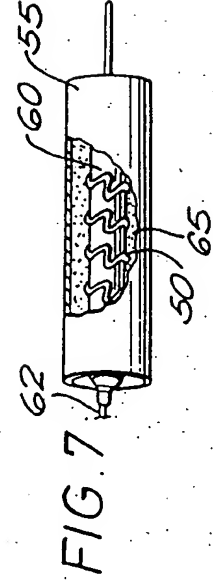
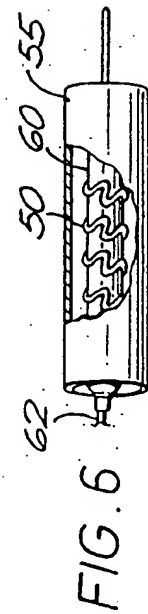
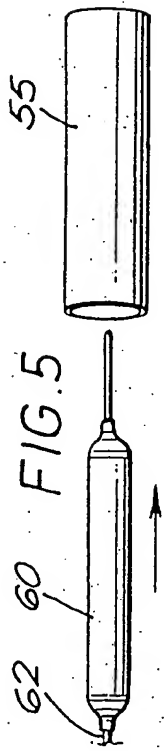
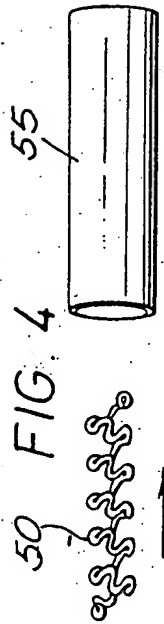
material.

7. A stent as claimed in any one of claims 1 to 6 comprising a fibrin in which residual coagulating protein has been neutralized.
8. A stent as claimed in any one of claims 1 to 7 wherein the fibrin contains a therapeutic substance.
9. A stent as claimed in claim 8 wherein said therapeutic substance is incorporated in microcapsules.
10. A stent as claimed in either of claims 8 and 9 wherein said therapeutic substance is selected from anticoagulant drugs, antiplatelet drugs, antimetabolite drugs and antimitotic drugs.
11. A stent assembly comprising a stent (20) as claimed in any one of claims 1 to 10 further comprising a catheter (10) having a balloon (15) at a distal end thereof, the stent being mounted on the outside surface of said balloon.
12. A method for making an intraluminal stent, the method comprising depositing fibrin on a stent substrate.
13. A method as claimed in claim 12 wherein fibrin is polymerized on said substrate.
14. A method as claimed in claim 13 wherein polymerization is effected by applying to said substrate successively (a) a solution of fibrinogen and (b) a solution of a fibrinogen-coagulating protein.
15. A method as claimed in claim 14 further comprising neutralizing the coagulating effect of residual coagulating protein.
16. A method as claimed in claim 15 wherein neutralization is effected by the addition of a thrombin inhibitor.
17. A method as claimed in any one of claims 14 to 16 wherein the fibrinogen-coagulating protein is selected from thrombin, reptilase and ancrod.
18. A method as claimed in any one of claims 13 to 17 further comprising the step of incubating the fibrin in a biological buffer solution.
19. A method as claimed in claim 12 wherein a fibrin preform is applied to said substrate.
20. A method as claimed in claim 19 wherein said

preform is a film.

21. A method as claimed in either of claims 19 and 20 wherein said preform is secured to said substrate with an adhesive.
22. A method as claimed in any one of claims 12 to 21 further comprising the step of affixing the stent onto a distal end of a catheter.
23. A method as claimed in claim 22 wherein the catheter is a balloon catheter and the stent is affixed upon the balloon thereof.
24. A method for making a intravascular device from fibrin comprising the steps of:
 - (a) admixing fibrinogen with a coagulating protein to produce fibrin;
 - (b) neutralizing the coagulating protein, and
 - (c) incubating the fibrin in a biological buffer solution.
25. A method as claimed in claim 24 wherein said coagulating protein is thrombin and a thrombin inhibitor is used for neutralizing the coagulating protein.
26. A method as claimed in claim 25 wherein said thrombin inhibitor is selected from hirudin and D-phenylalanyl-propyl-arginine chloromethyl ketone (PPACK).
27. A method as claimed in any one of claims 18 and 24 to 26 wherein said biological buffer solution comprises blood serum buffered with 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES).
28. The use of fibrinogen or fibrin for the manufacture of means for use in combatting restenosis.





EP 0 566 245 A1



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 30 1946

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 366 564 (TERUMO) -----		A61L31/00
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A61L A61F
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 15 JUNE 1993	Examiner PELTRE CHR.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPF FORM 1500 (01/92) (P0001)